An adaptive design for clinical trials with non-dichotomous response and prognostic factors ☆

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Abstract

We present an adaptive design for multi-arm clinical trials with bounded response and prognostic factors. The allocation is ruled by an urn model that fits a Robbins–Monro scheme. We obtain asymptotic properties for the performance and allocation of treatments.
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1. Introduction

Response-adaptive randomization in clinical trials mitigates the ethical problem of allocating patients to an inferior treatment by making the probability of assignment to this treatment smaller. Generalized Pólya urn models are a frequently used technique to perform this randomized adaptive designs. In Wei (1979) these models are applied in clinical trials with L treatments and dichotomous response. Each treatment is associated to a colour and patients are allocated to a treatment according to the proportion of its colour in the urn. If the treatment is a success, its colour is reinforced and if it is a failure, the rest of colours are reinforced. This scheme has been generalized in several ways (see, for instance, Rosenberger, 2002 and the references therein).

We study a randomized adaptive design to assign one of L treatments to patients that arrive sequentially. We suppose that these patients can be classified according to several prognostic factors or, without loss of generality, in $K + 1$ levels of one prognostic factor, although these levels are not used to stratify. The proportion of each level in the population is considered stable and, therefore, the probability that the next patient belongs to a particular level does not change throughout the trial. The patient's response is measured

by a bounded variable, which can be non-dichotomous. This response depends only on the treatment applied and on the patient's level, and it is independent of the response obtained for other patients. Patient's responses are used by means of replacement matrices to modify the composition of the urn. The next treatment is assigned according to $\mathbf{X}_n$, which is the vector of proportions of balls of each colour, or according to an adequate function of $\mathbf{X}_n$. This function is called 'urn function' and it helps to make the procedure more flexible.

The presence of prognostic factors in adaptive designs has been hardly considered in the literature. We use polytomous factors, but we assume two special characteristics. First, the prognostic factor is not used to balance the sample between the different strata of the population. Second, treatments are assigned independently of the patient's level. Therefore, we are considering prognostic factors in the same way as in Bandyopadhyay and Biswas (2001). Our approach generalizes the ideas of Bai et al. (2002), where a new adaptive design is proposed for a multi-arm clinical trial with dichotomous response, although they do not consider prognostic factors.

If we can assume that the effect of the patient's level in the performance of treatments is not too great, then it might be advisable to use the same urn to assign treatments to patients of all levels. This is not always the case. For instance, when prognostic factors are used to stratify, a different urn should be considered for each level, as suggested in Rosenberger and Lachin (2002), section 12.3. Besides, if we suspect that the effect of a level is too great (for instance, making a treatment, say A, better than B for this level, but worse than B for other level) then a different urn should be used for these levels, too.

Our goal is to determine the asymptotic behavior of this adaptive design when the same urn is used to randomize treatments. It can be proved that the sequence $\{\mathbf{X}_n\}$ follows an stochastic recurrence scheme of Robbins–Monro-type. Then, using similar techniques to those used in Higueras et al. (2006), and assuming additional conditions on the convergence of the replacement matrices, the a.s. convergence of $\mathbf{X}_n$ can be established and its limit can be explicitly obtained. All these procedures are developed in Section 2. The a.s. convergence of the replacement matrices depends on the a.s. convergence of the statistics used in their definition. In Section 3, the a.s. convergence of these statistics is proved. Besides, it is established that they are independent and normal, asymptotically. Finally, in Section 4, these results are illustrated with an extension to non-dichotomous response of a model presented in Moler et al. (2004).

2. Recurrence equation of the model

We are interested in an adaptive design of a clinical trial to compare $L \geqslant 2$ treatments, where the patients arrive sequentially and they can be classified according to a prognostic factor with $K + 1$ levels $0, \ldots, K$.

For each n, $n \geqslant 1$, we consider the variables:

$$\boldsymbol{\delta}_n = (\delta_{n1}, \ldots, \delta_{nL}), \quad \boldsymbol{\pi}_n = (\pi_{n0}, \ldots, \pi_{nK}),$$

where $\delta_{nj} = 1$, if treatment j has been applied, and $\delta_{nj} = 0$ otherwise, and where $\pi_{nk} = 1$, if the patient's level is k, and $\pi_{nk} = 0$ otherwise.

For every treatment j and patient's level k, the patient's response at stage n is modelled by a random variable Z_{njk}, that takes values in $[0, 1]$. $\mathbf{Z}_n$ is the $L \times (K + 1)$ matrix with entries Z_{njk}. The patient's response observed at stage n is

$$\sum_{j=1}^{L} \sum_{k=0}^{K} \delta_{nj} \pi_{nk} Z_{njk}. \tag{2.1}$$

In order to assign treatments, we consider an urn that contains balls of L different types. We assume that, initially, there are $\alpha > 0$ balls of each type. Let $\mathbf{X}_n = (X_{n1}, \ldots, X_{nL})$ be the proportion of balls of each type in the urn after stage n. Note that, for all n, $\mathbf{X}_n \in \Delta_{L-1}$, where $\Delta_{L-1} = \{\mathbf{x} \in \mathbb{R}^L : \sum_{i=1}^{L} x_i = 1, \ x_i > 0\}$. We consider $\varphi : \Delta_{L-1} \to \Delta_{L-1}$, and $\varphi(\mathbf{X}_n) = (\varphi_1(\mathbf{X}_n), \ldots, \varphi_L(\mathbf{X}_n))$. In particular φ can be the identity function. The $(n + 1)$th patient is assigned to treatment j with probability $\varphi_j(\mathbf{X}_n)$, $j = 1, \ldots, L$.